

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number  
WO 2004/014374 A1

(51) International Patent Classification<sup>7</sup>: A61K 31/437,  
A61P 25/28, 35/00, C07D 471/04

MILAN (IT). VULPETTI, Anna [IT/IT]; Via Volturno 80  
- Portici 3, I-20047 BRUGHERIO (IT).

(21) International Application Number:  
PCT/EP2003/007000

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,  
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,  
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 1 July 2003 (01.07.2003)

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

Published:

(26) Publication Language: English

— with international search report

(30) Priority Data:  
60/398,122 25 July 2002 (25.07.2002) US

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

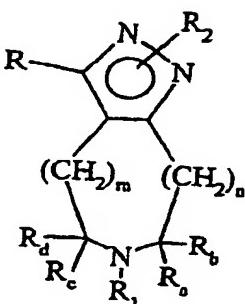
(71) Applicant (for all designated States except US): PHARMACIA ITALIA S.P.A. [IT/IT]; Via Robert Koch 1,2,  
I-20152 MILAN (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VILLA, Manuela  
[IT/IT]; Via San Bernardino 12, I-22040 LURAGO  
D'ERBA (Como) (IT). ABRATE, Francesca [IT/IT]; Via  
L. Settala 45, I-20124 MILAN (IT). FANCELLI, Daniele  
[IT/IT]; Via Montecuccoli 8, I-20147 MILAN (IT).  
VARASI, Mario [IT/IT]; Via Moncucco 24/a, I-20142

(54) Title: BICYCLO-PYRAZOLES ACTIVE AS KINASE INHIBITORS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

(57) Abstract: The present invention provides a method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a pyrazole-tetrahydro pyridine derivative. The invention also provides specific pyrazole-tetrahydro pyridines, a library comprising at least two of them, a process for their preparation and the pharmaceutical compositions containing them, which are useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, cell proliferative disorders, viral infections, autoimmune diseases and neurodegenerative disorders.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/07000

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/437 A61P25/28 A61P35/00 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US 2003/073672 A1 (TAYS KEVIN L ET AL) 17 April 2003 (2003-04-17) examples ---	13-18
P, X	WO 02 064574 A (ORTHO MCNEIL PHARM INC) 22 August 2002 (2002-08-22) page 11; examples 10,11 ---	13-18
X	WO 02 12242 A (PITTALA VALERIA ;VARASI MARIO (IT); FANCELLI DANIELE (IT); PHARMAC) 14 February 2002 (2002-02-14) claim 1; examples ---	1-30
A	WO 96 12720 A (PFIZER ;DUPLANTIER ALLEN J (US)) 2 May 1996 (1996-05-02) cited in the application examples ---	1-30
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

29 September 2003

Date of mailing of the International search report

27/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

Fazzi, R

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/07000

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	KIKUCHI, CHIKA ET AL: "Tetrahydrothienopyridylbutyltetrahydrobenzindoles: new selective ligands of the 5-HT <sub>7</sub> receptor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS (2002), 12(18), 2549-2552, 16 September 2002 (2002-09-16), XP002256018 page 2550; example 5G ---	13-18
X	SINGH, P. ET AL: "Quantitative structure-activity relationship studies on a new class of antihypertensive agents: derivatives of 3-aryl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine" QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS ( 1990 ), 9(1), 29-32 , XP001155089 figure 1; examples; table 1 ---	13-18
X	WINTERS, GIORGIO ET AL: "Synthesis, in vitro <sup>3</sup> H-prazosin displacement, and in vivo activity of 3-aryl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridines, a new class of antihypertensive agents" JOURNAL OF MEDICINAL CHEMISTRY ( 1985 ), 28(7), 934-40 , XP002256019 examples; tables I,,II,,III ---	13-18
X	RADINOV, R. ET AL: "3-Phenylpyrazolo[4,3-c]pyridine and derivatives: structure determination" JOURNAL OF MOLECULAR STRUCTURE ( 1987 ), 158, 99-108 , XP009018257 page 104; example 9 ---	13-18
A	LACKEY K K ET AL: "The discovery of potent cRaf1 kinase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 3, February 2000 (2000-02), pages 223-226, XP004188821 ISSN: 0960-894X page 224 ---	1-30
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/07000

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COHEN P: "The development and therapeutic potential of protein kinase inhibitors" CURRENT OPINION IN CHEMICAL BIOLOGY, CURRENT BIOLOGY LTD, LONDON, GB, vol. 3, no. 4, August 1999 (1999-08), pages 459-465, XP002216616 ISSN: 1367-5931 cited in the application figure 2 -----	1-30

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/07000

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/07000

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2003073672	A1	17-04-2003	NONE		
WO 02064574	A	22-08-2002	CA WO	2405532 A1 02064574 A2	22-08-2002 22-08-2002
WO 0212242	A	14-02-2002	AU BR CA CZ WO EP NO	8765401 A 0113176 A 2416527 A1 20030591 A3 0212242 A2 1320531 A2 20030381 A	18-02-2002 17-06-2003 14-02-2002 18-06-2003 14-02-2002 25-06-2003 24-02-2003
WO 9612720	A	02-05-1996	AU AU AU BR CN CZ EP FI HU WO JP NO NZ PL ZA	702105 B2 3531795 A 9240298 A 9504491 A 1161040 A ,B 9701200 A3 0787132 A1 954991 A 77517 A2 9612720 A1 9511758 T 971811 A 292991 A 319758 A1 9508839 A	11-02-1999 15-05-1996 21-01-1999 20-05-1997 01-10-1997 14-01-1998 06-08-1997 21-04-1996 28-05-1998 02-05-1996 25-11-1997 18-06-1997 25-02-1999 18-08-1997 21-04-1997